IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AF**
Nancy M. Lee *et al.*	Group Art Unit: 1636
Application No.: 10/690,880	Examiner: WALTER SCHLAPKOHL
Filed: October 22, 2003	Confirmation No.: 8369
For: BIOMARKER PANEL FOR COLORECTAL CANCER	

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Nancy M. Lee, Ph.D., hereby declare:

1. That I am a citizen of the United States of America, residing at 1830 Funston Avenue, San Francisco, California 94116.

2. That I have a Ph.D. in the field of biochemistry.

3. That my curriculum vitae is attached hereto as Exhibit A.

4. That I am a co-inventor of the application identified above.

5. That I have read and I am familiar with the above-identified application, including the Office Action dated July 25, 2007.

6. I understand that that Examiner is alleging that the pending claims lack written description for the terms:

(a) "independently validated control" or "validated control (of any kind)" (see, e.g., the Final Office Action at page 6); and

(b) "...an increase in at least one cDNA in the sample compared to cDNA levels from the independently validated normal control identifies the subject as a

candidate for the management of colorectal cancer and polyps..." (claim 57; Final Office Action at page 6).

However, it is also my understanding that the Examiner states in the Office Action mailed September 11, 2006, that the specification supports the use of "verified" normal counterparts (see, e.g., the Office Action of September 11, 2006).

The controls used in the invention are "validated" or "verified" as normal based upon a number of factors, all of which are routine in the art, including symptoms of various gastrointestinal diseases and disorder (e.g., colorectal bleeding, tissue morphology) as well as familial history and self history (FHSH) (see, e.g., American Journal of Epidemiology Vol. 141, No. 9: 863-871, 1995; attached hereto as Exhibit B). For example, paragraph [0026] of the specification provides support for the risk associated with subjects having a familial or self history of colorectal cancer as being 3-4x higher in the population. Accordingly, one of skill in the art would recognize that you would not want to include, as controls, those that have an increase risk or predisposition to the disease you are trying to detect. "Verified" and "validated" are synonymous when used in conjunction to the term "control". A "verified control," as the Examiner indicates, is supported by the application and refers to a subject that prospectively or retrospectively can be included as a normal control subject because the subject does not have or does not develop a cancer or polyp and lacks FHSH of such diseases. The term "validated control" also refers to a subject that prospectively or retrospectively can be included as a normal control subject and does not have or does not develop a cancer or polyp and lacks FHSH of such diseases. Samples taken from such subjects are indicative of a control population or "normals".

A person of ordinary skill in the art, based upon the disclosure and the information available in the art would recognize a "verified control" or "normal" for the purposes of the invention. Furthermore, although the term "validated control" is used in the specification (see, e.g., paragraph [0027]), the term is synonymous with "verified control," a term that the Examiner has indicated as supported by the specification.

The Examiner also alleges that the specification lacks written description for identifying a subject with an increase in expression of a biomarker as a candidate for colorectal cancer/polyp management. The Examiner is directed to the claims as-filed, which indicate that a change in a biomarker identifies a subject as a candidate for management (see, e.g., claims 49 and 56-58). Furthermore, the data as originally filed (see Figures 3A and 3C) show that an increase in IL-8 and COX2 are associated with colorectal cancer. Thus, an increase in the biomarkers of SEQ ID NO:1 and 2 (as recited in claim 49 as originally filed) indicate a subject for colorectal cancer management. As yet further evidence, Table 1 (below) indicates that IL-8, COX2 and SAA1 are increased relative to controls in human subjects thereby providing additional evidence (data supported and contemplated in the specification as-filed) that such subjects are at risk of having or having colorectal cancer. This includes an increase in SAA1 expression as claimed in the application at the time of filing.

6. I also understand the Examiner alleges that the claims are not enabled by the specification. For example, at page 10-11 of the Office Action mailed July 25, 2007, the Examiner alleges that because:

> "...the state of the art was underdeveloped both with respect to the use of nucleic acids to diagnose and manage disorder in general, as well as with respect to the use of nucleic acids for the management of patient care and discovery of therapeutic interventions for CRC and colorectal polyps in particular."

and

> ...while Applicant points to support in the specification to show that differences in gene expression were observed for panels of biomarkers in the context of normal and disease tissue in both a mouse MIN model of colorectal polyps and in human specimens, the biomarker panels are not comprised of the same biomarkers recited in the claims." Specifically, Applicants' claim 49 is drawn to the use of any two from the group. . .IL-8, PTGS-2 (COX2) and SAA1..."

Regarding the Examiner's first statement, the invention is an advancement of the technology that was previously available for the management of patient care. The invention identifies a number of markers indicative of colorectal cancer and polyps.

Regarding the Examiner's statements at page 10 that the data does not support the use of any 2 of the markers selected from the group consisting of IL-8, COX2 and SAA1 in methods or compositions for determining colorectal cancer or colorectal polyps in a subject (e.g., as set forth in claim 79), I contemplated based upon data available that the markers used and now claimed are indicative of colorectal cancer and polyps.

The development of colorectal cancer progresses through a series of stages. Initial morphology of the colon often appears normal, however, the data provided by the present application demonstrates that even in normal appearing mucosa of the colon, biological changes are taking place or have taken place. As these molecular changes occur, polyps are often produced, followed by cancerous lesions. Thus, it is important to identify these molecular changes in normal mucosa and polyps to identify the risk and development of cancerous lesions and provide patient care and management. In conception and reduction to practice of the disclosed invention, including the pending claims, a number of markers were identified that are useful for measuring the morphologically unseen, yet important changes, of the mucosa. Those markers included the polynucleotide and polypeptides listed in table of Figure 1 (these markers included IL-8, COX2 and SAA1). The original claimed invention includes a panel of these markers, as well as others. It is my understanding that the claimed invention was restricted to certain markers by the Patent Office for purposes of searching.

In further support of the invention as originally claimed and disclosed, as well as currently claimed, I provide the following additional data. This data corroborates and supports the original specification and data and the claimed invention.

The following data was obtained by rectal swab of subjects during colonoscopy. Swabs were obtained from normal appearing mucosa about 5-10 cm before the rectum of the subject. The swabs were stored in either PBS alone or in a media comprising RNAse inhibitors. RNA was isolated from the samples and RT-PCR'ed using the primers identified in the specification.

Validated controls were identified by determining the subject's family history and self history of cancer and the subject's own upper GI diseases and disorders. In addition, morphological identification of polyps and cancerous lesions identified during colonoscopy were also used to categorize subjects.

Multiple samples were obtained from each subject as described in paragraph 30 of the specification. In particular, 4 samples were obtained from each subject in the control, FHSH and polyp group. The value of "N", in Table 1, refers to the number of samples measured (e.g., 23 subjects x 4 samples per subject = 92). Each sample was measured for a number of markers, including those specifically identified in the application, as filed, using the primers and probes specifically identified in the application, as filed.

For example, for a single control subject, four samples were obtained by colorectal swab. RNA was isolated and RT-PCR was performed using primers, as described in the specification (i.e., SEQ ID Nos: 45-88), to amplify the biomarkers (SEQ ID NOs:1-22) identified in the application. The process of RT-PCR is described in the specification at paragraphs 31-38. Each reaction also contained a control marker (β-actin).

For quantitation of marker expression, the fluorescence of the SYBR Green dye (see, e.g., paragraph 34) bound to the PCR products was measured after each cycle, and the cycle numbers were recorded when the accumulated signals crossed an arbitrary threshold (CT value). To normalize this value, a ΔCT value was determined as the differences between the CT value for each marker and the CT value for β-actin or histidyl tRNA synthetase, which were repeated in each experiment as references and were shown not to vary significantly. For each marker a ΔΔCT value was determined as the difference between the ΔCT value for each individual sample and the average ΔCT for a gene obtained from the control samples. These ΔΔCT values were then used to calculated relative gene expression values as described in Applied Biosystems; User Bulletin 2; December 11, 1997). Thus, the "control" value is a ΔΔCT, a decrease in RNA between the control and a particular condition for a particular marker results in an increase of the ΔΔCT value

(indicative of reduced expression). Similarly, an increase in RNA between the control and a particular condition for a particular marker results in a decrease of the ΔΔCT value. Accordingly, a decrease in a ΔΔCT value is indicative of an increase in maker expression and an increase in ΔΔCT value is indicative of a decrease in maker expression. Looking at Table 1, for example, IL-8 in the control group has a ΔΔCT of 0.0050 and the cancer (PBS) group has a ΔΔCT of -3.191, an increase in IL-8 expression in the cancer group compared to control.

Table 1:

	N=	p21	PPAR-a	COX2	IL-8	CXCR2	OPN	COX1	Gro-a	Gro-g	PPAR-g	c-myc	CD44	mCSF-1	cyclin D	PPAR-d	SAA-1
Normal	92	0.0032	0.0002	-0.0016	-0.0050	-0.0022	0.0040	0.0010	-0.0003	0.0042	0.0030	0.0009	0.0015	-0.0018	0.0000	-0.0041	0.0017
FHSH	148	0.0084	0.0352	-0.1701	-0.0189	0.0400	-0.3756	-0.2055	-0.2925	-0.2518	0.0959	-0.6824	-0.4690	-0.4394	-0.3291	0.0662	-0.7372
polyps	100	0.1194	0.4066	-1.0155	-0.7688	-0.1969	-0.5657	0.0723	-0.5364	-0.3488	0.3836	-0.5599	-0.4329	-0.5711	-0.0130	0.0850	-1.0363
CA, PBS	49	1.15	0.936	-2.2796	-3.191	-1.761	-1.368	0.8802	-1.527	-2.181	1.371	-1.604	-1.196	-0.614	0.3896	0.4484	-2.223
CA, RNAP	62	0.761	0.21	-1.9662	-2.7	-0.12	-0.04	2.0847	-0.384	-1.104	0.188	-0.056	-0.082	0.434	0.0461	0.0944	-0.712

Normal = Subjects with no Family History or Self History of cancer (FHSH), no polyps, no colorectal cancer lesions, and no known upper GI diseases during colonoscopy.

FHSH = Subjects with a Family History or Self History of cancer (e.g., colorectal cancer), no polyps, no colorectal bleeding at the time of colonoscopy.

Polyps = Subjects with polyps with or without family or self history.

CA = Subjects with colorectal cancer.

CA(PBS) - Samples prepared in PBS.

CA(RNAP) - Samples prepared in RNA protection buffer.

White columns - Biphasic markers (e.g., an increase then a decrease during disease progression).

Dark grey - Markers with an increase in expression in polyps and colorectal cancer relative to normal controls.

Light grey - Markers with a decrease in expression in polyps and colorectal cancer relative to normal controls.

The data in Table 1, demonstrates that the markers identified in the specification (including those currently claimed as well as those subject to restriction requirement) can be used to identify subjects having colorectal cancer and polyps. In particular, IL-8 in the control population has ΔΔCT value of 0.0050 and in the cancer population (PBS) has a ΔΔCT value of -3.191; COX2 in the control population has a ΔΔCT value of -0.0016 and in a cancer population (PBS) has a ΔΔCT value of -2.2796; and SAA1 in the control population has a ΔΔCT value of 0.0017 and in the cancer population (PBS) has a ΔΔCT value of -2.223. These changes in value indicate a significant change in expression of the makers measured by RT-PCR.

As demonstrated by the data above, measuring at least two markers selected from IL-8, COX2 and SAA1 provides information regarding the subject's disposition and development of polyps or cancer. For example, (1) where an increase in IL-8 and COX2 is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (2) where an increase in IL-8 and SAA1 is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (3) where an increase in COX-2 and SAA1 is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (4) where an increase in IL-8, COX2 and SAA1 is present in the subject compared to control the subject has or is at risk of having colorectal cancer or polyps; and (5) where an increase and then a decrease in SAA1 is observed and an increase of IL-8 and/or COX2 is observed the subject had polyps and has transitioned to colorectal cancer. As indicated above, SAA1 is a biphasic marker meaning that it changes during disease progression; however, SAA1 is elevated compared to control both at the polyp and cancer stages.

Accordingly, the data demonstrate that the measurement of any two biomarkers selected from IL-8, COX2 and SAA1 provide evidence of colorectal cancer or polyps in a subject when compared to controls (as originally indicated, contemplated and claimed by the present application and currently claimed).

7. I further declare that all statements made on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 12/21/07

Nancy M. Lee (signature)

CURRICULUM VITAE

NANCY M. LEE

EDUCATION:

1963-67	Ph.D., Biochemistry University of Texas Austin, Texas
1960-63	B.S., Chemistry Southwestern University Georgetown, Texas

PROFESSIONAL EXPERIENCE

1995- present	Senior Scientist CPMC Research Institute California Pacific Medical Center San Francisco, CA
1989-1995	Professor, Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN
1987-89	Professor, Department of Pharmacology and Langley Porter Psychiatric Institute, University of California, San Francisco, CA
1984-87	Adjunct Assoc. Professor, Dept. of Pharmacology and Langley Porter Psychiatric Institute, University of California, San Francisco, CA
1978-84	Associate Research Pharmacologist, Department of Pharmacology and Langley Porter Psychiatric Institute, University of California, San Francisco, CA
1972-1978	Assistant Research Biochemist Department of Pharmacology and Langley Porter Psychiatric Institute, University of California, San Francisco, CA
1968-1972	Postgradraduate Research Biochemist III-VI

	Department of Pharmacology, University of California, San Francisco, CA
1967	Postdoctoral Fellow, Department of Biochemistry, Northwestern University, Evanston, Illinois
1963-1967	Research Assistant, University of Texas, Austin, Texas

SOCIETY MEMBERSHIPS

Sigma Xi (1972)
Society of Neuroscience (1974)
American Society for Pharmacology and Experimental Therapeutics (1976)
American Association for the Advancement of Science (1976)
Western Pharmacology Society (1981)
International Association of Women Bioscientist (1985)
Society of Chinese Bioscientists in America (1985)

AWARDS

American Heart Association Fellowship (1969 - 1972)

USPHS Research Scientist Career Development Award (1976-1981)

USPHS Research Scientist Award, K05 DA-00020: Beta-Endorphin Receptor and Dynorphin Receptor: Biochemical and Pharmacological Studies (1982-1994)

California Alliance for Mentally Ill Award (1984)

National Institute on Drug Abuse **MERIT** Award (1993 - 2003)

COMMITTEE ACTIVITY

National

Regular member for National Institute on Drug Abuse, Biomedical Research Committee (Washington, D.C.), 1980-83

Ad Hoc Committees for National Institutes of Health, National Science Foundation, Veterans Administration, and National Institute on Drug Abuse, 1980-present

Regular member for National Institute on Drug Abuse - Biomedical Research Committee, 1988-1993, Washington, D.C.

Chair for National Institute on Drug Abuse - Biomedical Research Committee, 1990 - 1993, Washington, D. C.

American Society for Pharmacology and Experimental Therapeutics - Regular Member, Committee on Drugs for Non-Medical Use, 1985-1989

Western Pharmacology Society, Secretary, 1985-1988

International Association of Women Bioscientists, Executive board member, 1985-present.

Regular member for National Institute of Mental Health - Neuropharmacology an Neurochemistry Committee, 1994-1998, Washington, D.C.

RESEARCH SUPPORT

Active Support

NIH R37-DA-02643 **(MERIT award)** Characterization and Regulation of Beta-Endorphin Receptor (1/81 - 7/03)

NIH P01-DA-08924, Opioid Peptide Analogs as Obstetric Analgesics (7/98-6/03)

NIH P01-DA11471, Non-opioid DynA: Molecular/Cellular/Physiological Studies (8/99-7/02)

Pending Support

NIH R01 NS057231-01 – The Role of Zinc in sporadic ALS

U.S. PATENTS

1. Therapeutic Uses of Dynorphin
   US Patent #4,361,553
2. Dynorphin Amide Analogs
   US Patent #4,462,941
3. Method for Controlling Blood Pressure
   US Patent #4,481,191
4. Clinical Usage of Dynorphin and Its Analogs
   US Patent #4,684,624
5. Method For Treating Cocaine Abuse
   US Patent Application # 08/476,691
6. Biomarker Panel for Colorectal Cancer
   US Patent Application
7. Drug Screening and Molecular Diagnostic Test for Early Detection of Colorectal Cancer, Reagents, Methods and Kits

PUBLICATIONS

Full Papers

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6. Kearney, E.B., Lee, N.M., Weidemann, I. and Kun, E.: The nature of inhibition of glutamate metabolism by incubation of liver mitochondria with ADP and 2,4-dinotrophenol and its prevention by a cytoplasmic factor. J. Physiol. Chem. Physics 1:575-583, 1969.

7. Skilleter, D.N., Lee, N.M. and Kun, E.: Malate dehydrogenases of ox kidney III. Comparison of the reactivity of sulfhydryl groups and their relationship to activities of the mitochondrial and cytoplasmic enzymes. Europ. J. Biochem. 12:533-539, 1970.

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27. Wu, Chuen-Shang C., Lee, N.M., Li, Choh Hao, Loh, H.H. and Yang, Jen Tsi: B-Endorphin: formation of α-helix in lipid solutions. Proc. Natl. Acad. Sci. 76:3656-3659, 1979.

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29 Stokes, K. Bradley, Lee, N.M. and Loh, H.H.: Mouse brain DNA-dependent RNA polymerases after chronic morphine treatment. J. Neurochem. 34:1058-1064, 1980.

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Neuronal Communication, Advances in Biochemical Psychopharmacology, (ed. E. Costa and M. Trabucchi), Raven Press 22:285-290, 1980.

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How accurate is self-reported family history of colorectal cancer?

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Much of the evidence that supports a relation between a positive family history of and increased risk for colorectal cancer is based on information obtained exclusively from patients. There have been few assessments of the accuracy of such data. The validity of self-reported family history of colorectal cancer was assessed in the course of a case-control study of colorectal adenomas conducted among patients aged 20-75 years who underwent colonoscopy in Brisbane, Australia between 1980 and 1985. Family histories reported by a subsample of 237 colonoscopy patients (74 cases and 163 controls) were compared with relatives' medical records and death certificates. Patients' reports of colorectal cancer in 90 relatives were confirmed for 70 (77.8%; 95% confidence interval (CI) 67.8-85.9). Among 124 reports by patients of relatives who had other abdominal cancer or bowel conditions, 114 (91.9%; 95% CI 85.7-96.1) were confirmed to be correct, while 10 (8.1%) were found to be colorectal cancer. Finally, 105 (99.1%; 95% CI 94.9-100.0) of a random sample of 106 completely negative reports by patients were confirmed to be correct. Overall, 77% of positive family histories (any positive relatives) were confirmed, and it was estimated that 98% of negative family histories (no positive relatives) were correct. Cases were slightly more accurate than controls in reporting both positive and negative histories among their relatives. By extrapolation of these results to the total sample of 1,244 patients in the larger case-control study, sensitivity of self-reported positive family history was estimated to be 0.87 among cases and 0.82 among controls, and specificity was estimated to be 0.97 in both groups.

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